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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
BRANNOCK M	
ART UNIT	**PAPER NUMBER**
1646	19

DATE MAILED: 08/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/370,358	Sklar et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D.	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jun 15, 2001

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-47 is/are pending in the applica

4a) Of the above, claim(s) 14 and 18-47 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-13 and 15-17 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5, 8

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Claims 1-47 are pending.

2. Applicant is notified that the amendments put forth in Paper 4, 11/1/99 and Paper 17, 06/15/01, have been entered in full.

3. Claims 14 and 18-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13, 2/5/01. Applicant is notified that claims 1-13, 15, 16, and 17 will be examined to the extent that the claims read on the elected species: a method of non-cellular solid phase display of 7-TM receptors, wherein receptor-ligand pairs are sorted by fluorescence. As no arguments have been presented as to why the restriction requirement may have been improper, the restriction requirement is made FINAL.

Claim Objections

4. Claim 4 is objected to because of the following informalities: the claim requires " an GPCR". To be grammatically correct, the claim should read "a GPCR". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-13, 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require the step of "incorporating an attachment scheme to a receptor" (see claim 1(a).) A "scheme" is not commonly known to be a physical entity, e.g. it is a design or plan. This limitation renders the claims indefinite because it is unclear what is encompassed by the term "scheme" and what is not encompassed by the term. Therefore, the metes and bounds of the claim cannot be determined.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 10-13 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of solid phase display of 7-TM receptors comprising the steps of solubilizing the receptor and presenting a ligand to bind the receptor, wherein a ligand for the receptor is known, does not reasonably provide enablement for said

method wherein a ligand for the receptor is not known. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims require the step of "presenting at least one ligand to bind to the receptor" (see claim 10). Therefore, the claims require that the receptor be capable of binding a ligand. It is well appreciated in the art of 7-TM receptor expression that many of these receptors loose the ability to bind a ligand after the receptors have been solubilized from the membranes of the cells in which they have been expressed. For example, this problem has been discussed by Eppler, MC *et al., J. Biol. Chem.* 267:22(15603-15612)92; see page 15610 last paragraph bridging page 15611, wherein the need to pre-bind the ligand prior to solubilization has been demonstrated for such 7TM receptors as the angiotensin II, vasopressin, parathyroid hormone, somatostatin and cholecystokinin receptors. This problem is a Catch-22 problem for the practice of the claimed invention. The specification contemplates the use of the invention in the process of ligand discovery (see pages 9, L11, for example). Thus one of ordinary skill in the art would appreciate that the invention was intended to be useful in the discovery of ligands for receptors wherein a ligand has not yet been identified (so called "orphan receptors"). However, to use the invention to screen for potential ligands, one would need to know that the solubilized receptor is capable of binding a ligand. Since many 7TM receptors require pre-binding of ligand before solubilization in order to retain activity, one of skill in the art would not know if the claimed invention would be useful for a given orphan receptor because neither its ligand nor its activity is known. One of skill in

the art would therefore have to perform extensive random trial and error experimentation to find a ligand for the receptor and then to determine if the receptor remained active after solubilization - as is required by the claims. Such a use of the invention is a "wish to know" type of use and is dependent on unduly burdensome trial and error experimentation. The specification has provided no guidance as to how one of skill in the art could tell whether or not a given orphan 7TM receptor could be used in the instant invention, and nor is such teaching available in the prior art

Therefore, due to the large quantity of experimentation required to identify ligands for receptors in order to use the receptors in the invention as claimed, the lack of direction and guidance provided in the specification regarding how to determine if a receptor without a known ligand could be used in the claimed invention, the contradictory and complex nature of the art wherein it is well appreciated that many and diverse 7TM receptors required ligand binding before solubilization to retain activity, see Eppler above, the scope of the claims which include any 7TM receptor, undue experimentation would be required of the skilled artisan to make and use the invention commensurate in scope to that which is claimed.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 10, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Robeva, AS et al., Drug Development Research 39(243-252)1996.

Robeva et al. disclose a method of displaying a 7TM receptor (Adenosine receptor) comprising incorporating an attachment scheme (e.g. hexahistadine tag) into the Adenosine receptor (GPCR construct), solubilizing the receptor by lysing membranes comprising the receptor (page 245) , presenting the receptor on a solid support (e.g. Ni-NTA agarose, page 245), wherein said method further comprises the step of combining the receptor and a ligand to accomplish binding (see page 244, col 2). Further, the step of incorporating an attachment scheme comprises incorporating the tag (coding sequence) into an oligonucleotide: see page 244, MATERIALS AND METHODS, wherein the method of subcloning the Adenosine receptor is referenced in Robeva et al., 1996, Biochem. Pharm. 51:545-555, wherein it is indicated that the tags are incorporated using a 30 base pair oligonucleotide, see Robeva et al., 1996, Biochem. Pharm, page 554. Further, Robeva, AS et al., Drug Development Research state that their method should be useful for other proteins and for a variety of methods including reconstitution assays (see page 554).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 6, 7, 8, are rejected under 35 U.S.C. 103(a) as being unpatentable over Robeva, AS *et al., Drug Development Research* 39(243-252)1996, as applied to claims 1-5, 10, and 15 above, in view of Jones, C. *et al.*, J. *Chromatography A* 707(3-22)1995.

Claims 6, 7, 8 require the elements of claims 1-5, 10, and 15 as discussed above, however claims 6, 7, 8, also require that the method comprise binding to a particulate substrate, e.g. silica beads. These additional limitations are well known variations of the solid phase display methods such as those disclosed by Robeva, AS et al. These variations are taught and discussed Jones, C. *et al.* wherein it is disclosed that a variety of substrates are commercially available as kits to perform these methods (see page ll, col. 1), such substrates beads, silica, etc. being available for the particular application contemplated (see page 5 and 19).

Therefore, it would be obvious to one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, to use a particulate substrate, e.g. silica beads, as taught by Jones, C. *et al.*, when practicing the general method taught by Robeva, AS *et al.*. The motivation to do so was provided by Jones et al. who teach that the selection of

appropriate support (e.g. substrate) is a matter of routine optimization of operating parameters depending on the specific receptor/ligand interaction of interest (see page 5).

12. Claims 12 and 13, are rejected under 35 U.S.C. 103(a) as being unpatentable over Robeva, AS *et al., Drug Development Research* 39(243-252)1996, as applied to claims 1-5, 10, and 15 above, in view of Jones, C. *et al.*, J. *Chromatography A* 707(3-22)1995 and Jayawickreme, CK. et al., Proc. Natl. Acad. Sci. 91(1614-1618)94.

Claims 12 and 13 require the elements of claims 1-5, 10, and 15 as discussed above, however claims 12 and 13 also require that the method comprise presenting a library of ligands to the receptor, and/or wherein the ligands are presented on a solid support. These additional limitations are well known variations of the solid phase display methods such as those disclosed by Robeva, AS et al. Specifically, Jones et al., discuss the general applicability of solid phase receptor assays for bimolecular recognition purposes (page 5 for example) and also that ligand libraries are useful (see page 17). Jayawickreme, CK. et al. disclose a particular a ligand library that is appropriate for 7TM receptors (e.g. G-protein coupled receptors, see the Abstract). Further, the ligand library taught by Jayawickreme, CK. et al. comprises ligands attached to supports which are released such that the individual ligands may interact with a receptor (see the Abstract).

Therefore, it would be obvious to one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, to use a ligand library designed for use

with 7TM receptors wherein the ligands are presented in conjunction with a solid support as taught by Jayawickreme, CK. et al, when practicing solid phase assays as taught by Jones et al., specifically, solid phase assays involving 7TM receptors as taught by Robeva, AS *et al.* The motivation to do so was provided by Jayawickreme, CK. et al. wherein it was stated that the use of the disclosed ligand library with G-protein coupled receptors can lead to the discovery of new ligands and therapeutic agents (see the Abstract).

13. Claims 9, 11, 16 and 17, are rejected under 35 U.S.C. 103(a) as being unpatentable over Robeva, AS *et al., Drug Development Research* 39(243-252)1996, as applied to claims 1-5, 10, and 15 above, in view of Szollosi, J. *et al.*, Cytometry 8(120-128)87

Claims 9, 11, 16, and 17 require the elements of claims 1-5, 10, and 15 as discussed above, however claims 9, 11, 16 and 17 also require that the method comprise labeling either the receptor (claim 9) or the ligand (11) or both with a fluorescent marker or sorting the bound receptor/ligand pairs by fluorescence (claim 16), such sorting being flow cytometry (claim 17). These additional limitations are well known variations of the receptor/ligand binding methods such as those disclosed by Robeva, AS et al. Szollosi et al. teach that FCET (Flow Cytometric Energy Transfer) is a well characterized technique for analyzing receptor/ligand interactions and sorting receptor-ligand pairs, comprising fluorescently labeling the receptor and the ligand and measuring the changes in fluorescence that occur during receptor/ligand binding (see the Abstract and page 120 and references therein).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success ~~label~~ to fluorescently label the ligand and receptor to sort receptor/ligand pairs based on fluorescence (as discussed by Szollosi et al.) after the 7TM receptors have been presented on a solid support as taught Rebova et al. above. The motivation to do so was provided by Szollosi et al. wherein it was stated that the disclosed FCET technique has several advantages including use with excess labeled ligands without washing thus enabling the investigation of relatively labile receptor-ligand complexes (see the Abstract).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler

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August 25, 2001